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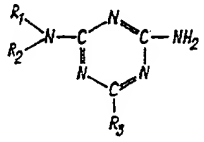
(54) 2-AMINO-4,6(SUBSTITUTED)-s-TRIAZINES AND METHODS FOR THEIR PREPARATION

(71) We, KAKENYAKU KAKO KABUSHIKI KAISHA, a Company registered under the Laws of Japan, of No. 7, 4-chome, Nihonbashi-Honcho, Chuo-Ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

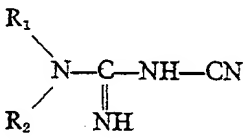
The present invention relates to novel s-triazine derivatives having the following general formula (I):



(I)

in which (a) R_1 is a phenyl radical, R_2 is an ethyl radical and R_3 is a pyridyl radical or an alkyl radical having from one to four carbon atoms, or (b) R_1 and R_2 together form a morpholino radical with the nitrogen atom with which they are combined and R_3 is an alkyl radical having from two to four carbon atoms.

The invention also provides salts of these derivatives and process for producing said s-triazine derivatives or their salts which comprises reacting a substituted dicyandiamide having the following general formula (II):

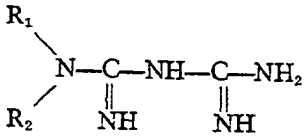


(II)

in which R_1 and R_2 have the same meaning as above, with a nitrile having the following general formula (III):

$$\_\_\_\_\_R_3CN \qquad \text{(III)}$$

in which R_3 has the same meaning as above, in the presence of a basic compound, or which comprising reacting a dicyandiamine with a secondary amine (IV) to get a substituted diguanide having the following general formula (V):



(V)

in which R_1 and R_2 have the same meaning as above, and then reacting the substituted diguanide of formula (V) with a carbonyl derivative having the following general formula (VI):

$$R_3—COR_4 \qquad \text{(VI)}$$

in which R_3 has the same meaning as above, and R_4 is a halogen atom (e.g. a chlorine or bromine), an amino radical, a hydroxyl radical, an alkoxy radical having from one to four carbon atoms, or —$OCOR_3$ radical (wherein R_3 represents group as defined above), in the presence of the basic compound identical or different from that in the former process as above.

The compounds (I) of the present invention may be used in pharmaceutical compositions and possesses a wide range of bioactivity in, for example, birds and mammals including humans. Their bioactivity remarkably increases the secretion of induced corticoid in the hormone system.

Moreover, the starting materials used in the process of the present invention are comparatively cheap and are available in large quantities; also, the yield of the process is excellent.

Examples of suitable substituted dicyandiamides of formula (II) include N - ethyl - N - phenyldicyandiamide; and N,N - (3 - oxapentamethylene) dicyandiamide.

Examples of suitable nitriles of formula (III) which can be used in the former process of the invention include: acetonitrile; propionitrile; n - butyronitrile; isobutyronitrile; 3 - cyanopyridine; and 4 - cyanopyridine.

In the former process, the inorganic or organic compound such as alkali metal carbonates, alkali metal hydroxides, metal alcoholates, alkali metal amides, tertiary amines or quaternary ammonium salts may be useful as the basic compound in the presence of which the reaction between the substituted dicyandiamide of formula (II) and the nitrile of general formula (III) is conducted. It is possible that the reaction will take place in the absence of a solvent, however, generally the reaction may better be carried out in the presence of the solvent. Hydrocarbons, ethers, ketones, alcohols and/or other organic solvents are used as the solvent, provided that the solvent does not interfere with the reaction, but β - hydroxyethyl methyl ether, β - hydroxyethyl ethyl ether, dioxane or butanol is particularly preferred. However, in the case where the nitrile of general formula (III) is used in excess quantity, a solvent need not be used in the reaction. The reaction may be effected at about 50 to 200°C, preferably near the temperature of reflux. The reaction will normally take from about 20 minutes to 24 hours to reach completion, at which time the s-triazine derivatives of formula (I) can be obtained in high yields.

In the latter process, a salt of the substituted diguanide of formula (V) can easily be produced by heating a salt of the secondary amine (IV), for example a hydrochloride, with the dicyandiamide either with or without a solvent such as water or alcohol. The substituted diguanide salt produced by this method need not necessarily be refined but can be used directly in the latter process of the present invention. When the free compound is required, it can be produced by any conventional method.

Examples of suitable substituted diguanides of formula (V) include ethylphenyldiguanide and N,N - (3 - oxapentamethylene)diguanide.

Examples of suitable carbonyl derivatives of formula (VI) which can be used in the latter process of the invention include: carboxylic acids, carboxylic acid esters such as ethyl acetate, ethyl propionate, ethyl n - butyrate, ethyl isobutyrate, ethyl nicotinate, ethyl isonicotinate, or alkyl esters of such acids and carboxylic acid anhydrides such as acetic anhydride, propionic anhydride, n - butyric anhydride or isobutyric anhydride.

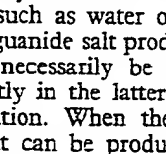
The reaction between the substituted diguanide of formula (V) or a salt thereof and the compound of general formula (VI) is conducted in the presence of a basic compound, such as an alkali metal carbonate, an alkali metal hydroxide, a metal alcoholate, an alkali metal amide, a tertiary amine, or a quaternary ammonium salt. The reaction may be carried out in the presence of a solvent such as hydrocarbons, ethers, ketones, alcohols, water and/or the other organic solvents provided that the solvent does not interfere with the reaction. It does not always follow that the reaction is maintained at constant temperature, but the temperature is preferably between −5°C and 150°C. Depending to the quantity of the batch, the reagents used, the temperature and the other conditions, the reaction will normally take from about 20 minutes to 70 hours to reach completion, at which time the s-triazine derivative of formula (I) can be obtained in high yields.

The s - triazines of formula (I) can be used in the form of a free base or as a salt produced by reacting the free base and an acid, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid, perchloric acid, formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, glycolic acid, nicotinic acid, tartaric acid, maleic acid, malic acid, lactic acid, pamoic acid, citric acid, ascorbic acid, methanesulphonic acid, salicylic acid, benzoic acid or cyclohexanesulphamic acid, or other pharmaceutically acceptable acids.

The effect of this invention is illustrated with reference to the pharmaceutical data.

R_1, R_2 and R_3 of the triazines to be obtained in the following examples and of other triazines to be obtained by similar methods are known in Table 1 as well as the melting points and code number provided with M signs.

TABLE 1

Product		R_3—	melting point (°C)
M5132	N-ethylanilino	3-pyridyl	185—186
M5103	N-ethylanilino	ethyl	136

The triazine derivatives (I) obtained by the method of this invention act on the hormone system, especially the system of diencephalone, pituitary gland and adrenal, and remarkably increase the secretion of the internally induced corticoid, mainly glucocorticoid.

ACTH and corticoid have a large variety of physiological and pharmaceutical effects, and thus they are used for medical purposes in various quarters; however, they are not free from secondary ill effects. The most serious disadvantage of the continuous administration of corticoid is supposed to be a decline in the performance of the adrenal cortex and a withdrawal syndrome.

ACTH shows the same effect as in the case of the administration of steroid, and one of its advantages is that the adrenal cortex performance is not decreased. Additionally it gives a well balanced secretion of corticoid from the adrenal cortex. However, it has serious disadvantages in that it can be used only by injection, it is extremely expensive, and it is not free from cases of death from shock. Thus its clinical application is radically restricted.

The merit of the novel compounds of our invention lies in the removal of the disadvantages of ACTH or corticoid while showing the desirable effects as shown by them.

Because of the effect of the compounds in increasing the secretion of internally induced corticoid, we can expect from it the same effect as from the administration of ACTH or corticoid in the case of the following diseases:

Nephrotic syndrome
Bronchial asthma
Chronic arthrorheumatism
Rheumatic fever
Chronic hepatitis
Allergic disease
Malignant lymphoma
Spinitis

and many other diseases that are susceptible to treatment by the administration of steroid agents.

The novel compounds (I) of the present invention can be applied in the form of any suitable medicinal composite in combination with other medicines as the case may be. It can be taken orally or otherwise. It can be administered in any pharmaceutically possible form, for instance, powder medicine, capsule medicine, pellet or granular medicine, injection medicine, or suppository.

From the data given above, we can claim that the triazine derivatives of the present invention provide a new important substitute medicine in the field of adrenal cortex steroid therapeutics.

The invention is illustrated but in no way limited by the following examples. The word "Cellosolve" used in the Examples is a Registered Trade Mark.

Example 1

2 - Amino - 4 - (N - ethylanilino) - 6 - (3 - pyridyl) - 1,3,5 - triazine

18.8 grams of N - ethyl - N - phenyldicyandiamide and 10.5 grams of 3 - cyanopyridine were added to a solution of 4 grams of potassium hydroxide in 60 ml of ethyl Cellosolve and the mixture was refluxed under stirring for 3 hours. The solution was then poured into about 500 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from acetonitrile. 19.5 grams of 2 - amino - 4 - (N - ethylanilino) - 6 - (3 - pyridyl) - 1,3,5 - triazine having a melting point of 185—186°C were thus obtained.

Elementary analysis for $C_{16}H_{16}N_6$:
Theoretical:
C 65.74%, H 5.52%, N 28.75%
Experimental:
C 65.53%, H 5.60%, N 29.00%

Example 2

2 - Amino - 4 - (N - ethylanilino) - 6 - ethyl - 1,3,5 - triazine

16.9 grams of N - ethyl - N - phenyldicyandiamide and 6.6 grams of propionitrile were added to a solution of 3.2 grams of potassium hydroxide in 40 ml of methyl Cellosolve and the mixture was refluxed under stirring for 2.5 hours. The solution was then poured into about 300 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from acetonitrile. 13.8 grams of 2 - amino - 4 - (N - ethylanilino) - 6 - ethyl - 1,3,5 - triazine having a melting point of 136°C were thus obtained.

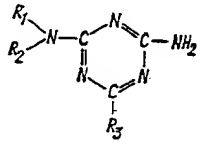
Elementary analysis for $C_{13}H_{17}N_5$:
Theoretical:
C 64.18%, H 7.04%, N 28.78%
Experimental:
C 64.49%, H 7.22%, N 28.76%

This 2 - amino - 4 - (N - ethylanilino) - 6 - ethyl - 1,3,5 - triazine was recrystallized from hydrochloric acid and the monohydrochloride was thus obtained.

Elementary analysis for $C_{13}H_{18}N_5Cl$:
Theoretical:
C 55.81%, H 6.49%, N 25.03%, Cl 12.67%
Experimental:
C 56.07%, H 6.48%, N 24.99%, Cl 12.82%

WHAT WE CLAIM IS:—

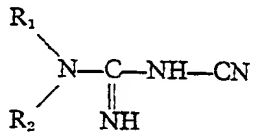
1. A compound of formula:



in which (a) R_1 is a phenyl radical, R_2 is an ethyl radical and R_3 is a pyridyl radical or an alkyl radical having from one to four carbon atoms, or (b) R_1 and R_2 together form a morpholino radical with the nitrogen atom with which they are combined and R_3 is an alkyl radical having from two to four carbon atoms.

2. 2 - Amino - 4 - (N - ethylanilino)-6 - ethyl - 1,3,5 - triazine or a monohydrochloride thereof.

3. A process for the preparation of a compound as claimed in claim 1, which comprises reacting a substituted dicyandiamide of formula:



in which R_1 and R_2 have the same meaning as in claim 1, with a nitrile of formula:

$$R_3CN$$

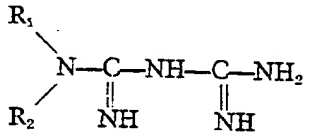
in which R_3 has the same meaning as in claim 1, in the presence of a basic compound.

4. A process according to claim 3, in which said substituted dicyandiamide is:

N - ethyl - N - phenyldicyandiamide or N,N - (3 - oxapentamethylene)dicyandiamide.

5. A process according to claim 3 or 4, in which said nitrile is: acetonitrile; propionitrile; n - butyronitrile; isobutyronitrile; 3 - cyanopyridine; or 4 - cyanopyridine.

6. A process for the preparation of a compound as claimed in claim 1, which comprises reacting a substituted diguanide of formula:



in which R_1 and R_2 have the same meaning as in claim 1 or a salt thereof with a carbonyl derivative of formula:

$$R_3COR_4$$

in which R_3 has the same meaning as in claim 1, and R_4 is a halogen atom, an amino radical, a hydroxy radical, an alkoxy radical with a chain of from one to four carbon atoms, or —$OCOR_3$ radical (wherein R_3 represents groups as defined above), in the presence of a basic compound.

7. A process according to claim 3 or 6, in which said basic compound is selected from alkali metal carbonates, alkali metal hydroxides, metal alcoholates, alkali metal amides, tertiary amines and quaternary ammonium salts.

8. A process according to claim 6, in which said substituted diguanide is: ethylphenyldiguanide or N,N - (3 - oxapentamethylene)-diguanide.

9. A process according to claim 6 or 8, in which a process for preparing said substituted diguanide comprises reacting a dicyandiamide with a secondary amine.

10. A process according to claim 6, in which said carbonyl derivative is: ethyl acetate; ethyl propionate; ethyl n - butyrate; ethyl isobutyrate; ethyl nicotinate; ethyl isonicotinate; acetic anhydride; propionic anhydride; n - butyric anhydride; isobutyric anhydride.

11. A process according to any one of claims 3 to 10, effected in the presence of hydrocarbons, ethers, ketones, alcohols and/or the other organic solvents.

12. A process according to claim 3 or 6, substantially as hereinbefore described with reference to any one of the foregoing examples.

13. A compound of formula (I), as hereinbefore defined, when produced by a process according to any one of claims 3 to 12.

14. A therapeutic composition which comprises a compound according to claims 1, 2 or claim 13 in association with a therapeutically acceptable carrier therefor.

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